

Remarks

The indication of allowable subject matter in claims 4, 25, and 27 is acknowledged with appreciation.

Claims 29 – 43 have been added to more particularly point out that which applicants regard as their invention.

Please cancel claim 27.

Claim 4 has been amended to make claim 4 an independent claim. New claim 29 is an independent claim incorporating all of the limitations of claims 1 and 27. Claims 30 – 41 depend from claims 4 and 29, and thus should be allowable for at least this reason.

Support for the claim amendments is found, for example, at page 27, lines 6 – 7; page 27, line 23; and in the claims as originally filed. Based on the above amendments and the following remarks, allowance is respectfully requested for pending claims 1 – 13, 25 – 26, and 28 – 42.

The rejection of claims 1 – 3, 5 – 9, 12, and 26 – 28 under 35 USC §103(a) over Bringman et al (DE 3819438 A1) and further in view of Van Wagenen et al (US 6,211,244) is respectfully traversed. According to the claimed invention, R on the phenyl group of the formulas [3], [4] and [5] represents a fluorine atom or trifluoromethyl group where the fluorine atom is defined as being not at the ortho position when R is a fluorine atom and n is 1. In other words, claim 1 recites that a single fluorine atom is at the meta or para-position on the phenyl group, which is clearly different from Bringman's disclosed fluorine atom at the ortho-position. Moreover, the claimed trifluoromethyl group (R) of the claimed invention is not disclosed nor suggested by Bringman.

Applicants unexpectedly found that the position-selective hydrogenolysis of the claimed substrate (i.e., the optically active secondary amine of formula [4]), in which R is a fluorine atom (in the meta- or para-position when n is 1) or trifluoromethyl group, proceeds efficiently to produce the target product (i.e., the optically active 1-(fluoro- or trifluoromethyl-substituted phenyl)ethylamine of the general formula [5]). This is in part due to electronic and steric effects involved in the position-selective hydrogenolysis. Therefore, the claimed hydrogenolysis is not obvious over the disclosure of Bringman as is further discussed below.

First, the electronic effect is demonstrated as Bringman's substituents of Ar, which are disclosed in example nos. 1-9 on page 5 of Bringman, are strongly electron-donating groups, and those (i.e., fluorine and chlorine), which are disclosed in example nos. 10-11, are weakly electron-attractive groups. In other words, strongly electron-attracting groups (such as trifluoromethyl group of the claimed invention) are not disclosed nor suggested as substituents of Ar in example nos. 1-11 of Bringman.

The previous Office Action requested support from within Bringman regarding the steric and electronic arguments. This is provided, in part, at page 4, lines 18 – 20, where Bringman states that the compound of general formula I is predominantly formed if the substituent has the function of increasing the electron density of the aromatic ring (Ar), and, in contrast, the decomposition selectivity from the compound of the general formula II to the compound of general formula I is reduced if the substituent does not have such function. It is known that a strongly electron-attracting group on an aromatic ring strongly reduces the electron density of the aromatic ring. Bringman's statement implies

that the position-selective hydrogenolysis from the compound of the general formula II to the compound of the general formula I would not proceed successfully, where the substituent of the aromatic ring is a strongly electron-attracting group. In contrast with Bringman, Applicants unexpectedly found that the claimed position-selective hydrogenolysis proceeds successfully by specifically selecting a strongly electron-attracting group, such as a trifluoromethyl group, as R in formula [4] in the claimed invention.

Secondly, the steric effect is explained below. An ortho-positioned fluorine is disclosed as a substituent of Ar in Bringman (see page 5, example no. 10). Because the ortho-position is closer to the breakage position (i.e., the position between nitrogen atom (N) and the chiral carbon (C*) bonded to phenyl in formula II of Bringman) in the hydrogenolysis than the meta- and para-positions, it is understood that the steric effect in the hydrogenolysis becomes the greatest by the ortho-positioned substituent. In other words, a person skilled in the art would not expect that the position-selective hydrogenolysis would proceed successfully using a substrate in which a meta- or para-position fluorine atom is a substituent of the phenyl group.

The Office Action notes Bringman example no. 6 as evidence that the steric effect is not shown in Bringman. In this example, the “Ar” ring is substituted with 3 electron-donating methoxy groups. As noted above, Bringman states that selectivity improves when the electron density of the aromatic ring is increased. The electron-donating character of the three methoxy groups appears to overcome the lack of a substituent in the ortho position.

Thus, the position-selective hydrogenolysis of the claimed invention is clearly not obvious over the disclosure of Bringman with respect to both the electronic effect and the steric effect. In other words, Applicants unexpectedly found that a position-selective hydrogenolysis proceeds successfully even by using the claimed substrate (i.e., the optically active secondary amine of formula [4]), in which R is fluorine atom or trifluoromethyl group, except for the ortho position when R is a fluorine atom and n is 1.

Van Wagenen does not cure the deficiencies of Bringman, as there is no specific disclosure of the compounds produced during the process of the claimed invention. Van Wagenen discloses thousands of inorganic ion receptor compounds in the various teachings of the reference. Although it might be possible, given sufficient guidance, to derive the optically active secondary amines of formula [4] from one of the many genera of structures taught by Van Wagenen, there is nothing to provide the necessary guidance. Van Wagenen specifically displays roughly 500 compounds in Figures 1a – 1r. None of the displayed compounds corresponds to the optically active secondary amines of formula [4] produced during the process of the claimed invention. Only with sufficient guidance or knowledge regarding a desired outcome would one of skill in the art identify the intermediates produced by the process of the claimed invention from within the broad teachings of Van Wagenen.

Additionally, Van Wagenen does not teach sodium borohydride as a hydride reducing agent for compounds within the claimed invention. Claim 2 requires the use of sodium borohydride as the reducing agent for reducing the imine of formula [3] to the optically active secondary amine of formula [4]. In

Van Wagenen, sodium borohydride is only disclosed as a suitable reducing agent for use during synthesis of compounds 8J, 8U, 11X, 12B – 12G, 12U, 12V, 12Z, 17M, 25 E, 25G, and 25Y. (Col. 30, lines 43 – 61; Col. 38, line 58 – Col. 40, line 37.) None of these compounds is similar to the optically active secondary amines corresponding to formula [4] in the claimed invention. In particular, these compounds lack one of the chiral carbons present in the compounds corresponding to formula [4]. Thus, Van Wagenen does not disclose or suggest use of sodium borohydride as a reducing agent according to the process of the claimed invention, and claim 2 should be allowable for at least this additional reason.

The rejection of claims 10, 11, and 13 as unpatentable over Hagitani (JP 09-278718) is also respectfully traversed. Claim 10 requires purification of an optically active 1-(3,5-bis-trifluoromethylphenyl)ethylamine of the formula [6]. By contrast, Hagitani discloses purification of a large family of phenethylamines. Substitution with trifluoromethyl is not specifically recited, as Hagitani only discloses substitution by haloalkyl groups. Additionally, the phenethylamine of Hagitani is not limited to a disubstituted one, but may be an unsubstituted or monosubstituted phenethylamine. Only with sufficient guidance or knowledge of a desired outcome would one of skill in the art select the compounds of the claimed invention from the broad genus suggested by Hagitani. Thus, claim 10 and its dependent claims should be allowed. Accordingly, withdrawal of the rejection of claims 10, 11, and 13 is respectfully requested.

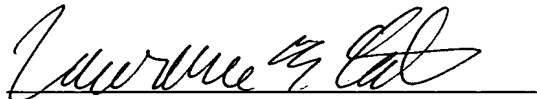
In view of the foregoing amendments and remarks, the application is respectfully submitted to be in condition for allowance, and prompt, favorable action thereon is earnestly solicited.

If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket #3007/49966).

June 13, 2003

Respectfully submitted,

A handwritten signature in black ink, appearing to read "J. D. Evans", written over a horizontal line.

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